

Organophosphorus insecticide poisoning

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ABSTRACT

INTRODUCTION: Acetylcholinesterase inhibition by organophosphorus insecticides can cause acute parasympathetic system dysfunction, muscle weakness, seizures, coma, and respiratory failure. Prognosis depends on the dose and relative toxicity of the specific compound, as well as pharmacokinetic factors. **METHODS AND OUTCOMES:** We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of oxime treatment for acute organophosphorus insecticide poisoning? We searched: Medline, Embase, The Cochrane Library, and other important databases up to October 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). **RESULTS:** At this update, searching of electronic databases retrieved 25 studies. After deduplication and removal of conference abstracts, 14 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of eight studies and the further review of six full publications. Of the six full articles evaluated, one update of a systematic review previously included in this review was added. We performed a GRADE evaluation for six PICO combinations. **CONCLUSIONS:** In this systematic overview, we categorised the efficacy for two comparisons based on information about the effectiveness and safety of oximes versus placebo or no oximes and oximes versus each other.

QUESTIONS

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INTERVENTIONS

OXIME TREATMENT FOR OP POISONING

Oximes versus each other (different oximes or different regimens of same oximes) 5

Unknown effectiveness

Oximes versus placebo or no oximes 4

Key points

- Acetylcholinesterase inhibition by organophosphorus insecticide results in accumulation of acetylcholine, which in turn causes enhancement and prolongation of cholinergic effects and depolarisation blockade (cholinergic crisis), muscle weakness, seizures, coma, and respiratory failure.
Prognosis depends on the dose and relative toxicity of the specific compound, as well as pharmacokinetic factors.
- Initial resuscitation, then atropine and oxygen, are considered to be the mainstays of treatment.
- There are consistent animal data supporting the effectiveness of oximes when given early to treat acute organophosphate insecticide poisoning. Against this background, we searched for RCTs and systematic reviews of RCTs on the effectiveness of oximes in people with acute organophosphate insecticide poisoning.
- We searched for **oximes versus placebo or no oximes** and for **oximes versus each other** (different oximes or different regimens of same oximes).
Oximes have not been shown to improve outcomes when compared with placebo, but most studies have been of poor quality, so a definite conclusion cannot be drawn.
We do not know how different regimens of oximes compare to each other as we found insufficient evidence.
- The value of oximes has been challenged in a systematic review of clinical trials ^[1] and in a Cochrane review, ^[2] which concluded, "Current evidence is insufficient to indicate whether oximes are harmful or beneficial in the management of acute organophosphorus pesticide poisoning".
- Results from published RCTs in people have differed from data taken from experimental animal studies. The results of one study indicate that solvents may play a crucial role in organophosphorus insecticide (and specifically dimethoate) toxicity. This could explain why oximes seem to be less effective clinically than in experimental studies where pure organophosphorus insecticide rather than marketed formulations, containing solvents, are often employed.

Clinical context

GENERAL BACKGROUND

Organophosphorus pesticide self-poisoning is an important clinical problem, particularly in rural regions of the developing world. It kills an estimated 200,000 people every year.

FOCUS OF THE REVIEW

The value of oximes has been challenged in recent literature. Despite this, there are consistent animal data supporting the effectiveness of oximes when given early. This overview will focus on the benefits and adverse effects of oximes for acute organophosphorus insecticide poisoning.

COMMENTS ON EVIDENCE

We identified one systematic review meeting our inclusion criteria. We don't know whether oximes are more effective than placebo at reducing mortality in people with acute organophosphorus insecticide poisoning. Compared with lower doses, higher-dose pralidoxime was associated with decreased mortality, although the difference did not reach statistical significance and the confidence intervals were wide. The review also found no significant difference between higher- and lower-dose pralidoxime in the proportion of people developing intermediate syndrome, or the proportion of people requiring ventilation. The review noted various issues with some of the RCTs, including poor reporting of methods, no account for factors that would affect outcomes, characteristics of participants in different groups not balanced at baseline, differing oxime doses and timing of treatment between studies, delays to treatment, and types of organophosphorus poison not being taken into account. Concerning oxime dosing regimen, only one RCT comparing pralidoxime treatment with placebo used doses of pralidoxime recommended by the World Health Organization (1999 update version).

SEARCH AND APPRAISAL SUMMARY

The updated literature search for this overview was carried out from the date of the last search, April 2010, to October 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 25 studies. After deduplication and removal of conference abstracts, 14 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of eight studies and the further review of six full publications. Of the six full articles evaluated, one update of a systematic review previously included in this review was added.

ADDITIONAL INFORMATION

There is currently mixed evidence regarding the effectiveness of the oximes, and some organophosphorus pesticides do not appear to respond well to oximes. Why might oximes be ineffective in published RCTs compared with experimental studies? The results of one study indicate that solvents may play a crucial role in organophosphorus insecticide (and specifically dimethoate) toxicity. This could explain why oximes seem to be less effective clinically than in experimental studies where pure organophosphorus insecticide, rather than marketed formulations containing solvents, are often used.

DEFINITION

Acute organophosphorus insecticide poisoning occurs after dermal, respiratory, or oral exposure. Following absorption, these compounds accumulate in fat, liver, kidneys, and salivary glands. Phosphates (P = O) are biologically active as acetylcholinesterase inhibitors, whereas phosphorothioates (P = S) need bio-activation to their phosphate analogues (oxons) to become biologically active.^[3] Oxons inhibit acetylcholinesterase by phosphorylation of the serine hydroxyl group in the substrate-binding domain of the enzyme. The rate of spontaneous reactivation of alkyl phosphorylated acetylcholinesterase depends on the chemical structure of the insecticide. Most of the commonly used organophosphorus insecticides carry either two methyl (e.g., demeton-S-methyl, dichlorvos, dimethoate, malathion) or two ethyl (e.g., chlorpyrifos, diazinon, parathion) ester groups attached to the phosphorus atom, so that dimethyl phosphorylated acetylcholinesterase or diethyl phosphorylated acetylcholinesterase, respectively, will be generated. Spontaneous reactivation of dimethyl phosphorylated acetylcholinesterase proceeds quite rapidly, so the patient's condition should improve even without oxime therapy. However, there is no such expectation of rapid recovery for patients intoxicated with diethyl phosphoryl insecticides. Inhibition of acetylcholinesterase at synapses results in accumulation of acetylcholine and over-activation of acetylcholine receptors at the neuromuscular junction and in the autonomic and central nervous systems.^[4] Early clinical features (the acute cholinergic crisis) reflect involvement of the parasympathetic system and include bronchorrhoea, bronchospasm, miosis, salivation, defecation, urination, and hypotension. Features indicating involvement of the neuromuscular junction (muscle weakness and fasciculations) and central nervous system (seizures, coma, and respiratory failure) are common at this stage. Respiratory failure may also occur many hours later, either separated in time from the cholinergic crisis — so-called 'intermediate syndrome'^[5] — or merged into the acute cholinergic crisis.^[6] The pathophysiology of this late respiratory failure seems to involve down-regulation of nicotinic acetylcholine receptors.^[5]^[6] Intermediate syndrome is particularly important because people who are apparently well can progress rapidly to respiratory arrest. A late motor or motor/sensory peripheral neuropathy can develop after recovery from acute poisoning with some organophosphorus pesticides.^[4] Acute poisoning may result in long-term neurological and psychiatric effects, but the evidence is still unclear.^[7]^[8] There are differences between pesticides in the clinical syndrome they produce and in the frequency and timing of respiratory failure and death.^[6]^[9]^[10]

**INCIDENCE/
PREVALENCE**

Most cases occur in the developing world as a result of occupational or deliberate exposure to organophosphorus pesticides.^[11] Although data are sparse, organophosphorus pesticides seem to be the most important cause of death from deliberate self-poisoning worldwide, causing about

200,000 deaths each year.^[12] For example, in Sri Lanka, about 10,000 to 20,000 admissions to hospital for organophosphorus poisoning occur each year. Of these, at least 10% die. In most cases, the poisoning is intentional.^[13] Case mortality across the developing world is commonly more than 20%.^[12] In Central America, occupational poisoning is reported to be more common than intentional poisoning, and there are fewer deaths.^[14]

AETIOLOGY/ RISK FACTORS	The widespread accessibility of pesticides in rural parts of the developing world makes them easy options for acts of self-harm. ^[12] Occupational exposure is usually because of insufficient or inappropriate protective equipment. ^[11]
PROGNOSIS	There are no validated scoring systems for categorising severity or predicting outcome of acute organophosphorus poisoning. The highly variable natural history and difficulty in determining the dose and identity of the specific organophosphorus compound ingested make predicting outcome for an individual person inaccurate and potentially hazardous because people admitted in good condition can deteriorate rapidly and require intubation and mechanical ventilation. Prognosis in acute self-poisoning is likely to depend on dose and toxicity of the organophosphorus compound that has been ingested (e.g., neurotoxicity potential, half-life, rate of ageing, whether activation to a toxic compound is required [e.g., parathion to paraoxon: pro-poison], and whether it is dimethylated or diethylated [see Definition]). ^[10] ^[15] Prognosis in occupational exposure is better because the dose is normally smaller, the route is dermal, and the compound more easily identified.
AIMS OF INTERVENTION	To prevent mortality; to reduce rates of intubation (with or without ventilation), pneumonia, and delayed polyneuropathy; and to reduce the duration of ventilation and intensive care.
OUTCOMES	Mortality; pneumonia; intermediate syndrome; delayed polyneuropathy; need for ventilation, including rates of intubation, and duration of ventilation or intensive care; adverse effects.
METHODS	<p>Search strategy <i>BMJ Clinical Evidence</i> search and appraisal date October 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to October 2014, Embase 1980 to October 2014, The Cochrane Database of Systematic Reviews 2014, issue 4 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. Inclusion criteria Study design criteria for inclusion in this systematic overview were systematic reviews and RCTs published in English, including 'open' (non-blinded) RCTs, and containing at least 20 individuals, of whom more than 80% were followed up. There was no minimum length of follow-up. <i>BMJ Clinical Evidence</i> does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. Evidence evaluation A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed <i>a priori</i> with our expert contributor. In consultation with the expert contributor, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our pre-defined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' section. Adverse effects All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although <i>BMJ Clinical Evidence</i> presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. Comment and Clinical guide sections In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As <i>BMJ Clinical Evidence</i> does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. Structural changes this update At this update, we have removed the following interventions from this overview: atropine; benzodiazepines to control organophosphorus-induced seizures; glycopyrronium bromide (glycopyrrolate); removing contaminated clothes and washing the poisoned person; activated charcoal (single or multiple dose); alpha₂ adrenergic receptor agonists; butyrylcholinesterase replacement therapy; extracorporeal clearance; gastric lavage; magnesium sulphate; milk or other home remedy immediately after ingestion; N-methyl-D-aspartate receptor antagonists; organophosphorus hydrolases; sodium bicarbonate; cathartics; ipecacuanha (ipecac). At this update, we have focused on the following question: What are the effects of oxime treatment for acute</p>

organophosphorus insecticide poisoning? **Data and quality** To aid readability of the numerical data in our overviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions in this overview (see table, p 9). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *BMJ Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of oxime treatment for acute organophosphorus insecticide poisoning?

OPTION OXIMES VERSUS PLACEBO OR NO OXIMES

Mortality

Oximes compared with placebo or no oximes We don't know whether oximes are more effective than placebo or no oximes at reducing mortality in people with acute organophosphorus insecticide poisoning. Evidence was weak and contradictory, and it was difficult to draw reliable conclusions (low-quality evidence).

Intermediate syndrome

Oximes compared with placebo or no oximes We don't know whether oximes are more effective than placebo or no oximes at reducing intermediate syndrome in people with acute organophosphorus insecticide poisoning (low-quality evidence).

Need for ventilation

Oximes compared with placebo or no oximes We don't know whether oximes are more effective than placebo or no oximes at reducing the need for ventilation in people with acute organophosphorus insecticide poisoning (low-quality evidence).

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 9.

Benefits:

We found one systematic review (search date 2009)^[2] of oximes in people with organophosphorus poisoning, which identified seven RCTs (845 people). Three of the RCTs (366 people), reported in four publications,^{[16] [17] [18] [19]} compared pralidoxime treatment with placebo. Reporting of methods in the RCTs was poor. The review noted that many studies did not account for factors that would affect outcomes. In some studies, characteristics of participants in different groups were not balanced at baseline. Only one RCT^[17], comparing pralidoxime treatment with placebo, used doses of pralidoxime recommended by the World Health Organization (at least 30 mg/kg loading dose, then 8 mg/kg/hour intravenous infusion).^{[20] [21]}

Oximes versus placebo or no oximes

The review carried out a meta-analysis of three RCTs (366 people) comparing oxime treatment with placebo for the outcomes of mortality and ventilation requirement.^[2] Oximes were given either as a dose of 4 g to 12 g infused daily over 3 days without a loading dose, or as a 2 g-loading dose over 20 minutes followed by a constant infusion of 0.5 g/hour for a maximum of 7 days. The review found no significant difference between treatment with an oxime and placebo in mortality (3 RCTs: 366 people; 47/186 [25%] with oxime treatment v 22/180 [12%] with placebo; OR 2.68, 95% CI 0.93 to 7.72) or need for ventilation (3 RCTs: 70/186 [38%] with oxime treatment v 50/180 [28%] with placebo; OR 2.00, 95% CI 0.81 to 4.95). The review authors noted that the different oxime doses used in the studies and differences in the types of organophosphate poison meant that meta-analysis might not produce a true estimate of effect. One of the RCTs (110 people) identified by the review also reported the proportion of people developing intermediate syndrome.^{[18] [19]} It found that an infusion of pralidoxime 12 g over 3 days significantly increased the proportion of people developing intermediate syndrome compared with placebo (36/55 [65%] with pralidoxime v 19/55 [35%] with placebo; OR 3.59, 95% CI 1.64 to 7.88). However, baseline differences in this RCT suggested that people allocated to treatment with an oxime might have been more severely poisoned compared with those allocated to placebo.^[2]

Harms:

One RCT included in the systematic review found that, compared with placebo, pralidoxime significantly increased tachycardia, hypertension, systolic blood pressure, and diastolic blood pressure

after the loading dose at 20 minutes (all P values <0.0001), and significantly increased tachycardia at 72 hours (P <0.0001) and hypertension (P = 0.005).^[17]

Comment:

Oximes (such as pralidoxime, obidoxime, and HI-6) reactivate **acetylcholinesterase** (AChE) inhibited by organophosphorus insecticides,^{[15] [20]} as they have a molecular structure that 'fits' the surface of the inhibited enzyme. The extent of reactivation by oximes depends upon the chemical form of inhibited AChE, the nature and concentration of oxime present at the site, and the length of time the oxime is present. Phosphorylated enzyme may become aged by partial de-alkylation of the serine group at the active site of AChE. The **rate of ageing** depends on the structure of the organophosphorus compound. **Ageing** of the phosphorylated enzyme leads to an inactive enzyme, after which reactivation is no longer possible. Re-synthesis of new enzyme in the liver is required if AChE activity is to return to normal. Oximes are only of benefit as long as some of the inhibited AChE remains in the un-aged form.

It is commonly, but erroneously, believed that within 1 day of intoxication virtually all the inhibited AChE is in the 'aged' form so that oxime therapy, if employed, would be useless. However, there are good biochemical reasons for suggesting that, as soon as an effective concentration of oxime is achieved, the balance of 'ageing' and reactivation of inhibited AChE is altered in favour of the latter. Thus, progress towards complete inhibition may be slowed markedly. It is probable that benefit will ensue, even if oxime therapy is commenced or continued several days after intoxication has occurred.^[3] It may take several days for the pesticide concentration to drop below the point at which the rate of reactivation surpasses re-inhibition.^[15] In-vitro and in-vivo studies indicate that oximes can reactivate acetylcholinesterase;^{[15] [22]} however, in-vitro studies have also revealed mechanisms whereby oximes may be detrimental.^[23] Thus far, clinical trials have not yet provided conclusive evidence concerning the clinical benefit or harm from oximes.

One large prospective cohort study examining treatment with pralidoxime for 802 people with chlorpyrifos, dimethoate, or fenthion self-poisoning found that acetylcholinesterase inhibited by the two dimethyl organophosphorus pesticides, dimethoate and fenthion, responded poorly to pralidoxime.^[10] By contrast, acetylcholinesterase inhibited by the diethyl organophosphorus pesticide chlorpyrifos responded well to pralidoxime.^[10] Further studies are required to determine whether this variation in response is true for all dimethyl and diethyl organophosphorus pesticides, and for higher doses of oximes.

Adverse effects

Adverse effects of oximes include hypertension, cardiac dysrhythmias (including cardiac arrest after rapid administration), headache, blurred vision, dizziness, and epigastric discomfort.^[24] Such adverse effects with pralidoxime have been reported only with either rapid administration or doses greater than 30 mg/kg bolus. It may be difficult to distinguish these adverse effects from the effects of the organophosphorus insecticide.

Clinical guide

There is currently mixed evidence regarding the effectiveness of the oximes, and some organophosphorus pesticides do not appear to respond well to oximes. Why might oximes be ineffective? A study performed in mini-pigs using orally administered, clinically relevant doses of agricultural emulsifiable concentrate (EC) dimethoate, dimethoate active ingredient alone, or solvents found that administration of agricultural dimethoate EC, but not saline, caused respiratory arrest within 30 minutes, severe distributive shock, and neuromuscular junction dysfunction that was similar to human poisoning.^[25] Moderate toxicity resulted from poisoning with dimethoate active ingredient alone or the major solvent cyclohexanone. Combining dimethoate with cyclohexanone reproduced severe poisoning characteristic of agricultural dimethoate EC poisoning. A formulation without cyclohexanone showed less mammalian toxicity. These results indicate that solvents play a crucial role in organophosphorus insecticide (and specifically dimethoate) toxicity. This could explain why oximes seem to be less effective clinically than in experimental studies where pure organophosphorus insecticides, rather than marketed formulations, are often employed. World Health Organization guidelines (1999 update version) recommend giving high doses of oxime (pralidoxime chloride 30 mg/kg bolus followed by 8–10 mg/kg/hour or obidoxime 250 mg bolus followed by 750 mg/24 hours, until at least 12 hours after atropine is no longer required) to all people with organophosphorus poisoning.^{[20] [21]}

OPTION

OXIMES VERSUS EACH OTHER (DIFFERENT OXIMES OR DIFFERENT REGIMENS OF SAME OXIMES)

Mortality

Oximes versus each other (different oximes or different regimens of same oximes) We don't know whether different regimens of pralidoxime differ in effectiveness at reducing mortality in people with acute organophosphorus insecticide poisoning (**low-quality evidence**).

Intermediate syndrome

Oximes versus each other (different oximes or different regimens of same oximes) We don't know whether different regimens of pralidoxime differ in effectiveness at reducing intermediate syndrome in people with acute organophosphorus insecticide poisoning (low-quality evidence).

Need for ventilation

Oximes versus each other (different oximes or different regimens of same oximes) We don't know whether different regimens of pralidoxime differ in effectiveness at reducing the need for ventilation in people with acute organophosphorus insecticide poisoning (low-quality evidence).

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 9 .

Benefits:

We found one systematic review (search date 2009) ^[2] of oximes in people with organophosphorus poisoning, which identified seven RCTs (845 people). Four of the RCTs (479 people), reported in four publications, ^[26] ^[27] ^[28] ^[29] compared different doses of pralidoxime. Reporting of methods in the RCTs was poor. The review noted that many studies did not account for factors that would affect outcomes. In some studies, characteristics of participants in different groups were not balanced at baseline. Additionally, oxime doses and timing of treatment differed among the studies, there were delays to treatment, and the type of organophosphate poison was not considered. The review carried out meta-analyses for studies that reported comparable outcomes.

Higher doses versus lower doses of oxime

The review carried out a meta-analysis of four RCTs (479 people) comparing higher doses with lower doses of oximes for the outcome of mortality. ^[2] The review found that, compared with lower doses, higher-dose pralidoxime was associated with decreased mortality, although the difference did not reach statistical significance and the confidence intervals were wide (4 RCTs; 13/256 [5%] with higher-dose pralidoxime v 25/223 [11%] with lower-dose pralidoxime; OR 0.38, 95% CI 0.10 to 1.47). The review also found no significant difference between higher- and lower-dose pralidoxime in the proportion of people developing intermediate syndrome (3 RCTs: 32/160 [20%] with higher-dose pralidoxime v 30/123 [24%] with lower-dose pralidoxime; OR 0.94, 95% CI 0.24 to 3.62) or the proportion of people requiring ventilation (2 RCTs: 88/136 [65%] with higher-dose pralidoxime v 105/136 [77%] with lower-dose pralidoxime; OR 0.72, 95% CI 0.08 to 6.35).

It should be noted that treatment regimens varied across studies. One RCT compared a 12 g reducing infusion given over 4 days (high dose) with a 1 g bolus of pralidoxime (low dose). ^[26] ^[27] In a second RCT, all participants were given a 2 g-loading dose of pralidoxime intravenously followed by either a high-dose regimen (24 g per day for 2 days) or a low-dose regimen (6 g per day for 2 days). Both groups were then given 6 g pralidoxime per day (1 g per 4 hours) until weaned off ventilation. ^[30] The third RCT compared two intramuscular regimens of pralidoxime, with the high dose being roughly double the low dose and both being reduced over time. ^[28] The fourth RCT compared three different dosing regimens, each modified according to estimated severity of poisoning, with different routes of administration (intravenous or intramuscular or both). ^[29]

Harms:

One RCT included in the review reported that no substantial adverse effects (such as nausea, vomiting, or diastolic hypertension) were noted in trial participants; however, both diastolic and systolic blood pressure were significantly higher over the first 24 hours in the high-dose group compared with the standard bolus group (mean systolic [mmHg]: difference 20.6, 95% CI 19.0 to 22.2; mean diastolic [mmHg]: difference 8.3, 95% CI 7.2 to 9.5). ^[30]

Comment:

In one observational clinical study of a different oxime (obidoxime), a high-dose regimen (8 mg/kg bolus, then 2 mg/kg/hour infusion) produced hepatitis in 3/12 (25%) people. ^[31] Two of six deaths were because of liver failure. The use of pralidoxime (30 mg/kg loading dose, then 8 mg/kg/hour infusion) in eight people in the same study did not produce hepatitis. A more recently developed oxime (HI-6) has also been used in humans, with no reported adverse effects. ^[32]

Clinical guide

There is currently mixed evidence regarding the effectiveness of the oximes, and some organophosphorus pesticides do not respond well to oximes. World Health Organization guidelines (1999 update version) recommend giving high doses of oxime (pralidoxime chloride 30 mg/kg bolus followed by 8–10 mg/kg/hour or obidoxime 250 mg bolus followed by 750 mg/24 hours, until at least 12 hours after atropine is no longer required) to all people with organophosphorus poisoning. ^[20] ^[21] One RCT comparing constant infusion with a bolus regimen found that the former reduced morbidity and mortality in people with moderately severe poisoning. ^[30]

GLOSSARY

Acetylcholinesterase An enzyme that cleaves acetylcholine.

Pro-poisons Some organophosphorus pesticides require activation *in vivo* to become toxic.

Ageing Esterases (such as acetylcholinesterase and neuropathy target esterase) are inhibited by organophosphorus compounds through phosphorylation. Inhibited acetylcholinesterase reactivates spontaneously at very slow rates; oximes speed up this reaction. However, phosphorylated acetylcholinesterase may lose an alkyl side chain non-enzymatically, leaving a hydroxyl group in its place ('ageing'). Regeneration is then no longer possible. The half-life is 33 hours for diethyl pesticides such as chlorpyrifos.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Rates of ageing The rate depends on the identity of the alkyl side chains on each organophosphorus. Those with two methyl groups will age faster than those with two ethyl groups and thus become unresponsive to oximes at an earlier time point.

SUBSTANTIVE CHANGES

Oximes versus each other (different oximes or different regimens of same oximes) Review restructured. One systematic review updated.^[2] Categorisation unchanged (unknown effectiveness).

Oximes versus placebo or no oximes Review restructured. One systematic review updated.^[2] Categorisation unchanged (unknown effectiveness).

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TABLE GRADE evaluation of interventions for organophosphorus poisoning

Important out-comes	Mortality, pneumonia, intermediate syndrome, need for ventilation, adverse effects									
	Number of stud-ies (participants)	Outcome	Comparison	Type of ev-idence	Quality	Consisten-cy	Directness	Effect size	GRADE	Comment
What are the effects of oxime treatment for acute organophosphorus insecticide poisoning?										
3 (366) ^[2]	Mortality	Oximes v placebo or no oximes	4	−1	0	−1	0	Low	Quality point deducted for weak methods of included RCTs; directness point deducted for lower than recom-mended dose used in some studies, affecting gener-alisability of results	
1 (110) ^[2]	Intermediate syn-drome	Oximes v placebo or no oximes	4	−2	0	0	0	Low	Quality points deducted for sparse data and weak methods (imbalance in treatment groups in baseline severity)	
3 (366) ^[2]	Need for ventilation	Oximes v placebo or no oximes	4	−1	0	−1	0	Low	Quality point deducted for weak methods of included RCTs; directness point deducted for lower than recom-mended dose used in some studies, affecting gener-alisability of results	
4 (479) ^[2]	Mortality	Higher doses v lower dos-es of oxime	4	−1	0	−1	0	Low	Quality point deducted for weak methods of included RCTs; directness point deducted for variation in doses assessed, affecting generalisability of results	
3 (283) ^[2]	Intermediate syn-drome	Higher doses v lower dos-es of oxime	4	−1	0	−1	0	Low	Quality point deducted for weak methods of included RCTs; directness point deducted for variation in doses assessed, affecting generalisability of results	
2 (272) ^[2]	Need for ventilation	Higher doses v lower dos-es of oxime	4	−1	0	−1	0	Low	Quality point deducted for weak methods of included RCTs; directness point deducted for variation in doses assessed, affecting generalisability of results	
Type of evidence: 4 = RCT; 2 = Observational Consistency: similarity of results across studies. Directness: generalisability of population or outcomes. Effect size: based on relative risk or odds ratio.										